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The relationship between CD3+ and CD4+ T lymphocyte ratio and rejection & infection in renal transplantation patients

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Abstract
Aim: In our study, we aimed to investigate the changes in T lymphocyte markers the infections seen after renal transplantation and rejection diagnosis and the differential diagnosis.
Material and Methods: A total of 56 patients were enrolled in follow-up after renal transplantation. They were hospitalized due to failure in renal function tests of 31 patients were divided into two groups with clinical and laboratory features of infection and rejection. As the control group who had come to the examination of infection after renal transplantation and rejection were 25 patients without rejection doubt. 10 patients in control group had transplantation from cadaveric donors. In serum samples of patients with T-lymphocyte markers, CD3, CD4, CD8 levels were studied by flowcytometrical methods. Surface markers of T lymphocytes relationship with clinical infection and rejection were investigated
Results: CD3, CD4 and CD8 cells in terms of infection and rejection were not significantly different between the two groups. The cell surface determinants were similar to the groups of infection and rejection of transplant recipients and the control group. However cadaveric donor organ transplant recipients CD3, CD4 and CD8 levels were significantly decreased compared to infection and rejection groups. Lymphocyte markers and WBC lymphocytes ratio in the first and second tracking infection and rejection group when compared to the values, were not statistically different.
Discussion: Renal transplant recipients and especially after induction therapy with ATG measured monitoring the levels of T lymphocytes may provide clinical benefits, in critical cases of infection and rejection may be suggestive.

Keywords
Renal Transplantation, acute rejection, infection, CD3, CD4, CD8.

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Introduction

End-stage chronic renal failure (ESRD) is a health problem with high morbidity and mortality, the incidence of which is increasing every year in our country and around the world. Today, three renal replacement therapy models are applied to patients with ESRD. These treatment models are hemodialysis, peritoneal dialysis and renal transplantation, respectively. As of 2013, the number of patients diagnosed with ESRD in Turkey exceeded 70 thousand. While the majority of these patients receive dialysis treatment, only around 2500 – 3000 patients receive renal transplantation annually throughout the country [1].

According to the United States Renal Database System (USRDS) data, when ESRD patients who underwent renal transplantation were compared with patients on the national waiting list receiving dialysis treatment, it was shown that patients who underwent renal transplantation had a 68% lower risk of death after 3 to 4 years of follow-up [2]. Meta-analyses have shown that renal transplantation is the main and most important form of treatment in ESRD patients, with higher quality of life and lower morbidity and mortality rates compared to dialysis treatments [2, 3].

With the influence of the development and diversity of drugs used after renal transplantation, 5-year graft survival rates have reached 95% in living donor transplants and 89% in cadaver transplants. The survival rates of the patients were found to be 95% and 91%, respectively. The main causes of mortality after transplantation are cardiovascular diseases and infection [2-4]. As kidney transplantation becomes more common, the increase in post-transplant problems has led to transplant recipients being considered a "special patient group". Minimizing the problems that this special patient group may encounter after transplantation should be one of the main goals of transplantation treatment, and the main ways to achieve this are the selection and preparation of patients to be transplanted, post-transplant follow-up, and early diagnosis and intervention of conditions such as rejection/infection [2-4]. Today, there are no markers that will allow us to make a definitive diagnosis of rejection after renal transplantation. A biopsy may still be needed to diagnose rejection. Again, differentiating infection from rejection after renal transplantation is also an important problem. Infection and rejection can sometimes occur together, making this a more complex problem [5, 6]. In this study, we asked, "What is the role of T lymphocyte markers in the diagnosis and differential diagnosis of rejection/infection in patients who have undergone renal transplantation and present to the clinic with infection/rejection findings? Is there an increase or decrease in T lymphocyte subgroups among these clinical conditions?", "Immunosuppression." We aimed to find answers to questions such as "What is the difference between the dose and the change in lymphocyte subgroups?"

Material and Methods

This study was approved by the Ethics Committee of Çukurova University Faculty of Medicine (Date: 04/04/2013, No: 18/5). This prospectively planned study included 56 patients who were followed up after renal transplantation by Çukurova University Faculty of Medicine Organ Transplantation Center between January 2010 and March 2014. The patients were informed about the study and an informed signed consent form approved by the Çukurova University Scientific Research Projects Board (project number: TF2013LTP19) was obtained. During the hospitalization period, 3 cc blood samples were taken from these patients into a complete blood count tube with the preliminary diagnosis of infection/rejection. As a control group, 15 patients without any suspicion of rejection/infection, who applied to the Urology outpatient clinic of Çukurova University Faculty of Medicine and came for follow-up after renal transplantation, were included in the study.

Patients admitted to our clinic had fever, tenderness in the transplanted kidney, edema, decreased urine output, weight gain, elevated white blood cells, an increase of 0.3 mg/dl/day or more in serum creatinine, and proteinuria. Renal biopsy was performed in 2 patients and rejection was diagnosed. Since the patients in the other rejection group did not accept biopsy, rejection treatment was given. Renal function tests improved with immunosuppressive therapy.

Clinical findings, urine and blood cultures were used as basis for distinguishing infection/rejection groups. Four of the patients in the infection group had positive urine cultures and four had positive blood cultures, and antibiotics were given in accordance with the culture. Of the patients with urine culture growth, 3 had ESBL (+) Staph Aureus growth and 1 had Strep agalactia growth. Of the patients with blood culture growth, 2 had ESBL (+) Klebsiella pneumonia, 1 had Acinetobacter baumanii, and 1 had Staph Hominis growth. Empiric antibiotic therapy was given to 4 patients whose cultures showed no growth, based on complete urinalysis. Kidney function tests improved with antibiotic treatment. Of the patients with no growth in their cultures and normal urinalysis, 3 had lung infection and 2 had spondylodiscitis.

In the cadaver group, patients who were transplanted from cadavers and used ATG (anti-thymocyte globulin) as immunosuppressant were included.

All patients were monitored daily for physical examination, temperature, pulse, blood pressure, urine amount, complete blood count and blood biochemistry. CD3, CD4, CD8, CD45 levels were taken as the first follow-up, along with a complete blood count before treatment, when the patients were hospitalized. T lymphocyte marker levels, which were checked again at the end of the treatment, were taken as the second follow-up and these parameters were compared.

In the patient and control groups, complete blood count, SDM, CRP, PCT, BUN, creatinine and drug level (Tacrolimus) were studied in the Central laboratory of Çukurova University Faculty of Medicine. CD3, CD4, CD8, CD45 were examined by flow cytometry method in the immunohematology laboratory.

Statistical analysis

SPSS 17.0 package program was used in the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (median and minimum - maximum where necessary). Chi Square test or Fisher test statistics were used to compare categorical variables. Distributions were checked when comparing continuous measurements between groups. Since the data

were not distributed parametrically, the Mann Whitney U test was used in comparisons. The first and second follow-up results of lymphocyte ratios in CD3, CD4, CD8 and WBC were evaluated with the Wilcoxon test. For $p < 0.05$, the results were considered statistically significant.

Results

The average age of the 56 patients included in the study is 34.8±13.4 years and the range is from the lowest to 7 and the highest to 70. The patients participating in the study were evaluated in four groups: infection group (n = 17), rejection group (n = 14), control group (n = 15) and cadaver group (n = 10). The average age of patients in the infection arm was 34.8±18.7, the average age of patients in the rejection group was 36.6±11.0, the average age of patients in the control group was 32.2±7.9, and the average age of patients in the cadaver group was 37.6±14.2 (Table 1) (p=0.898). The groups were similar in terms of age.

58.8% (33) of all patients were male and 41.2% (23) were female. As for gender distribution of the groups, 52.9% of the patients in the infection arm, 50.0% of the patients in the rejection group, and 80.0% of the patients in the cadaver group were male. In the control group, the rate of male patients was 66.7%. There was no difference between the groups in terms of gender (p = 0.573) (Table 1).

The distribution of lymphocyte ratios in WBC among the groups and the T lymphocyte markers CD3, CD4, CD8 were examined (Table 2). When we examined the CD3 cell values by groups, the CD3 median value of the patients in the infection arm was 74.0 (52.0-93.7), the CD3 median value of the patients in the rejection arm was 83.4 (54.0-94.5), and the CD3 median value of the patients in the control group was 54.2 (34.7-74.7). When the groups were evaluated in terms of CD3, there was no statistical difference between the infection, rejection and healthy control groups. However, the CD3 median value of the cadaver group was statistically significant and lower than the other groups (Table 2).

When we examine CD4 cell values by groups, the median CD4 value of patients in the infection group is 43.5 (21.5-53.3), the median CD4 value of patients in the rejection group is 40.6 (24.0-68.1), and the median CD4 value of patients in the control group is 39.4 (32.6-58.5), and the median CD4 value of the

Table 1. Gender and age distribution by groups

	Groups				p value
	Infection	Rejection	Control	Cadaver	
Age Med (Min-Max)	30,0 (7-70)	33,5 (24-58)	31 (20-50)	29 (27-58)	0,898
Gender n (%)					
Male	9 (52,9)	7 (50,0)	10 (66,7)	8 (80,0)	0,573
Female	8 (47,1)	7 (50,0)	5 (33,3)	2 (20,0)	

Table 3. Distribution of laboratory parameters of patients in the Infection and Rejection groups

	Infection Med (Min - Max)	Rejection Med (Min - Max)	p values
Height (cm)	161 (130,0 - 184,0)	165 (150,0 - 176,0)	0,728
Weight (kg)	69 (24,0 – 93,0)	64,5 (27,0 – 88,0)	0,822
HCT	33 (27-37,4)	32 (24-46)	0,83
Hgb	11 (9,0-12,6)	11 (8-15)	0,497
Platelet	316.000 (215.000 - 600.000)	213.500 (110.000 – 400.000)	0,006
WBC	10500 (6400 – 30000)	8000 (2500 - 21000)	0,224
AST	18 (13-50)	14 (7-26)	0,122
ALT	32 (14-139)	19 (9-40)	0,203
BUN	13 (2,3-51,0)	37,5 (15-116)	0,001
Creatinin	1,0 (0,5-3,1)	2,2 (0,9-14)	0,004
CRP	1,0 (0,0-16,0)	2,0 (0,0-38,0)	0,418
Procalcitonin	0,2 (0,0-1,1)	0,5 (0,1-10)	0,06
Sedimentation	22,5 (10-78)	25,5 (10-36)	0,734

Table 2. Distribution and comparison of T lymphocyte markers by groups

Groups	CD3 Med (Min - Max)	CD4 Med (Min - Max)	CD8 Med (Min - Max)	Lymphocyte ratio in WBC
Infection (n=17)	74 (52-93,7)	43,5 (21,5-53,3)	35,1 (19-59)	15,8 (5,6-37,0)
Rejection (n=14)	83,4 (54-94,5)	40,6 (24-68,1)	38,8 (20,0-63,2)	14,5 (1,8-28,0)
Control (n=15)	84,0(70-92)	39,4(32,6-58,5)	45,7 (32,0-58,3)	20,6 (13,9-27,8)
Cadaver (n=10)	54,2 (34,7-74,7)	29 (20-38,5)	38,7 (27,7-48,0)	1,7 (1,0-2,1)
p values				
Infection vs. Rejection	0,257	0,886	0,448	0,637
Infection vs. Control	0,078	0,74	0,017	0,054
Infection vs. Cadaver	0,04	0,011	0,548	0,0001
Rejection vs. Control	0,652	0,88	0,425	0,041
Rejection vs. Cadaver	0,007	0,019	0,964	0,001
Control vs. Cadaver	0,001	0,004	0,197	0,0001

patients in the cadaver group was 29.0 (20.0-38.5). When the groups were evaluated in terms of CD4, there was no statistical difference between the infection, rejection and healthy control groups. However, the CD4 median value of the cadaver group was statistically significantly lower than the other groups (Table 2).

When we examined the CD8 cell values by groups, the CD8 median value of the patients in the infection arm was 35.1 (19.0-59.0), the CD8 median value of the patients in the rejection arm was 38.8 (20.0-63.2), the CD8 median value of the patients in the control group was 45.7 (32.0-58.3), and the median CD8 value of patients in the cadaver group was 38.7 (27.7-48.0). When the groups were evaluated in terms of CD8, it was determined that the only statistical difference was between the infection group and the healthy control group. The CD8 median value of the control group was statistically significantly higher than the infection group (Table 2).

When we examined the lymphocyte ratio in the WBC of the patients according to groups, the median value of the lymphocyte ratio in the WBC of the patients in the infection group was 15.8 (5.6-37.0), the median value of the lymphocyte ratio in the WBC of the patients in the rejection group was 14.5 (1.8-28.0), the median value of the lymphocyte ratio in the WBC of the patients in the control group was 20.6 (13.9-27.8), and the median value of lymphocyte ratio in WBC of patients in the cadaver group was 1.7 (1.0-2.1). When the groups were evaluated in terms of the lymphocyte ratio in WBC, there was no statistical difference between the infection group, the rejection group and the control group. The lymphocyte ratio in WBC of the control group was statistically significantly higher than the rejection group. The median value of lymphocyte ratio in WBC of the cadaver group was statistically significantly lower than the other groups (Table 2).

Patients in the infection group and rejection group in the study were examined in detail. Comorbid conditions, clinical features in the perioperative period, treatments applied and laboratory results were recorded. The two groups were similar in terms of general demographic and clinical information distributions.

Patients in the infection group and rejection group in the study were evaluated in terms of HLA compatibility, height, weight and laboratory parameters. When HLA compatibility was considered, 3/6 tissue compatibility was the most common in all groups. There was no difference between the groups in terms of PRA class 1 and class 2.

The platelet, BUN and creatinine values measured during the first follow-up were statistically different between the groups.

While the platelet median value of the infection group is 316000 (215000-600000), the platelet median value of the rejection group is 213500 (110000-400000). The first follow-up platelet value of the infection group was statistically significantly higher than the rejection group (p = 0.006).

While the median BUN value of the infection group was 13.0 (2.3-51.0), the median BUN value of the rejection group was 37.5 (15-116) (p=0.0001). The first follow-up BUN value of the infection group was statistically significantly lower than the rejection group. While the creatinine median value of the infection group is 1.0 (0.5-3.1), the median creatinine value of the rejection group is 2.2 (0.9-14.0). The first follow-up creatinine value of the infection group was statistically significantly lower than the rejection group (p = 0.004) (Table 3).

The first and second follow-up results of T lymphocyte markers of the patients followed in the study were evaluated according to groups. In the second follow-up, it was possible to measure the values in 8 of 17 patients in the infection group and in 10 of 14 patients in the rejection group. As for the lymphocyte ratios in WBC, it was possible to measure the second follow-up values in 5 of 17 patients in the infection group and in 6 of 14 patients in the rejection group.

When the groups were examined one by one over time, the change in the ratio of CD3, CD4 and CD8 cells and lymphocytes in WBC between the first and second follow-ups was not significant.

When the infection group was compared with the rejection group, there was no statistical difference in the ratio of CD3, CD4, CD8 cells and lymphocytes in WBC at both the first and second follow-up.

The CD4/CD8 ratio was calculated based on the T lymphocyte marker results of the patients followed in the study. The median value of the CD4/CD8 ratio of patients in the infection group was 1.2 (0.4-2.3), the median value of the CD4/CD8 ratio of patients in the rejection group was 1.1 (0.4-2.8), the median value of the CD4/CD8 ratio of patients in the control group was 0.8 (0.6-1.8), and the median value of the CD4/CD8 ratio of patients in the cadaver group was 0.6 (0.5-1.1). There was no statistical difference between the groups in terms of CD4/CD8 ratio (p = 0.151).

In terms of the second follow-up laboratory blood measurement results of the infection and rejection groups, only the BUN values were statistically different as a result of the comparison between the groups in the second measurement. While the median BUN value of the infection group is 16 (9-61), the median BUN value of the rejection group is 37 (21-149). The first follow-up BUN value of the infection group was statistically significantly lower than the rejection group (p = 0.006). The second follow-up measurements were compared with the first follow-up measurements, and the change over time (post-treatment) was examined. However, there was no statistically significant difference.

Discussion

Renal transplantation is currently the main treatment option in the treatment of end-stage renal failure patients, as it does not only prolong life but also improves the quality of life, eliminates the morbidity associated with dialysis treatments, and has a lower cost in the long term [7, 8].

Segundo et al investigated the relationship between the number of T regulatory cells in peripheral blood and graft survival. In the 5-year follow-up of 90 patients who underwent renal transplantation, they observed that graft survival was 6-12 months longer with high T regulatory cell levels (70% and above) [9]. T regulatory cells may play a role in antagonizing the inflammatory state and may be considered a good prognostic factor associated with kidney transplantation.

Peddi et al demonstrated that intermittent thymoglobulin therapy based on peripheral blood CD3 T lymphocyte count is safe and associated with a low rejection rate in kidney

transplant recipients. Patients with end-stage renal disease have lower peripheral T and B cell counts than the healthy population. Ultra-low dose Thymoglobulin reduces peripheral lymphocytes in a dose-dependent manner. This dose-dependent approach will help develop optimal treatment strategies in renal transplant recipients [10]. In our study, the median CD3 T lymphocyte value in the group receiving induction therapy with ATG was found to be statistically significantly lower than the other groups. The main goal of induction therapy with ATG is to reduce the risk of acute rejection in the first week after organ transplantation. Indeed, while induction therapy provides a lower rate of acute rejection, it also poses a higher risk for infections and malignancies [11-13]. These complications have been associated with depletion of peripheral T cells due to excessive immunosuppression and low pretransplantation thymus function [14, 15].

Gurkan et al examined the recovery kinetics of T cell subsets following ATG treatment in adults and children. In adults, peripheral CD4+ T cell counts decreased by 85% after treatment with ATG, while recovery of the count began approximately 2 weeks later. After 2 months, an increase of up to 35% of the basal level was observed. On the other hand, when looking at CD8+ T cells, ATG administration only resulted in a 22% reduction. Complete recovery of T lymphocyte numbers takes up to 6 months. It did not detect any change in peripheral CD4 + or CD8 + T lymphocyte numbers in patients who were not given ATG [16]. In our study, the number of CD4+ T lymphocytes was found to be statistically significantly lower in the ATG-administered group compared to the other groups. No statistically significant difference was found in terms of CD4+ T lymphocytes in the infection, rejection and control groups. When the groups were evaluated in terms of CD8+ T lymphocytes, it was determined that the only statistical difference was between the infection group and the control group. It was found that the CD8+ T lymphocyte median value of the control group was statistically significantly higher than the infection group. Based on this finding, we think that the infection developed due to the decrease in cytotoxic CD8+ T lymphocytes in the infection group. In a study conducted by Welzl et al. in CMV seronegative patients, they showed that immunosuppressive treatment did not affect the number of CD8+ T lymphocytes, but there was a moderate increase in the number of CD4+ CD28+ T lymphocytes compared to the control group [17].

Machado et al. found that treatment management based on peripheral CD3 + T lymphocyte count in ATG monitoring after renal transplantation was 45% less drug used and 20% less costly than WBC count [18]. In our study, the decrease in the lymphocyte ratio in WBC and the decrease in the CD3+ T lymphocyte median value in patients given ATG compared to other groups supports this literature.

Ordonez et al. showed that in renal transplant recipients, the risk of acute rejection increased 6-fold with high levels of CD45RC expression on CD8+ T lymphocytes examined before transplantation. By using this biomarker, risk can be determined, the immunosuppressive regimen can be adjusted accordingly and the patient's quality of life can be improved [19].

Identification of Th9, Th17, Th22 cells increased the number of different subsets of CD4+ T cells. It appears that Th17 cells and Th1 and Th2 cells play an important role in allograft rejection. In clinical and experimental studies conducted in the last 10 years, IL-17 has been shown to have a role in allograft rejection [20].

CD4 lymphopenia (<300/mm3) has been identified as an objective marker of excessive immunosuppression. CD4 lymphopenia has been determined as a risk factor for post-transplant neoplasms (skin cancer and post-transplant lymphoproliferative disorder), opportunistic infections and cardiovascular complications [21]. In another study investigating the number of CD4+ T lymphocytes and the frequency of genitourinary tumors, no significant relationship was found [22].

Berg et al evaluated groups of kidney transplant patients in their 5-year follow-up and showed that there was a relationship between the decrease in the number of CD8 + lymphocytes and their dysfunction. Again, in this study, no significant change was detected in CD4+ T lymphocyte subgroups (memory and regulatory) [23]. In our study, it was observed that the CD8+ T lymphocyte ratio decreased in all other groups compared to the control group. The CD8 median value of the control group was found to be statistically significantly higher than the infection group.

In a study by Torio et al., the measurement of intracellular ATP levels in CD4+ T lymphocytes was evaluated, based on the idea that the intracellular ATP level would increase in activated T lymphocytes. Intracellular ATP levels in kidney transplant patients who developed infection were found to be lower than in the control group and the rejection group. This may explain the increase in opportunistic infections due to immunosuppression. However, no significant difference was found between the rejection group and the healthy population or stable patients [24]. In another study, while intracellular ATP level decreased in case of infection, no significant relationship was found between tacrolimus and cyclosporine levels and intracellular ATP level [25].

To be the reason why the lymphocyte ratio in WBC was found to be significantly lower in the cadaver group compared to other groups. Again, the statistically significant increase in the lymphocyte ratio in WBC of the control group compared to other groups shows the adequacy of immunosuppressive treatment.

Conclusion

Considering the literature, our study is one of the few studies examining T cell subtypes in patients who have undergone renal transplantation in our country. Appropriate parameters are needed to enable early diagnosis and early treatment of acute renal allograft rejection. Monitoring T lymphocyte levels by flow cytometric method during the follow-up of induction therapy with ATG was found to be significant in terms of evaluating the adequacy and effectiveness of treatment. Failure to detect significant differences in the levels of T lymphocyte markers in the differential diagnosis of infection/rejection may be due to the small number of patients. Studies on larger patient groups are needed to clearly determine the clinical importance of T cell subtypes in patients who have undergone renal transplantation and to fully understand their impact on prognosis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content

including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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